Original article

Omalizumab and the risk of malignancy: Results from a pooled analysis

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Background: Since initial registration, the omalizumab clinical trial database has expanded considerably, with a doubling of patients exposed in the clinical trial environment. Previous pooled data (2003) from phase I to III studies of omalizumab showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%). The previous analysis was based on limited available data, warranting further investigation.

Objective: We sought to examine the incidence of malignancy using comprehensive pooled data from clinical trials of omalizumab-treated patients.

Methods: This pooled analysis included data from 67 phase I to IV clinical trials. The prespecified primary analysis assessed the incidence of primary malignancy in 32 randomized, double-blind, placebo-controlled (RDBPC) trials.

Results: There were 11,459 unique patients in all clinical trials (7,789 received omalizumab). The primary analysis identified malignancies in 25 patients (RDBPC trials): 14 in 4,254 omalizumab-treated patients and 11 in 3,178 placebo-treated patients. Incidence rates per 1,000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 (95% CI, 2.26-6.94) and 4.45 (95% CI, 2.22-7.94), respectively; the corresponding rate ratio was 0.93 (95% CI, 0.39-2.27). Primary malignancies were of varying histologic type and occurred in a number of different organ systems; no cluster of histologies was identified.

Conclusions: In this pooled analysis no association was observed between omalizumab treatment and risk of malignancy in RDBPC trials; the rate ratio was below unity. The data suggest that a causal relationship between omalizumab therapy and malignancy is unlikely. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: *Asthma, allergy, IgE, anti-IgE, omalizumab, malignancy, pooled analysis*

Omalizumab (Xolair; Genentech, South San Francisco, Calif, or Novartis, East Hanover, NJ), a humanized anti-IgE mAb, is approved as an add-on therapy for the treatment of inadequately controlled severe persistent allergic (IgE-mediated) asthma in adults, adolescents, and children (≥6 years of age) in the European Union[1] and in adults and adolescents (≥12 years of age) with moderate-to-severe persistent allergic asthma in the United States.[2] Omalizumab prevents the binding of IgE to receptors on mast cells, thus inhibiting the generation of a resultant cascade of inflammatory mediators and consequent symptoms in susceptible subjects.[3-9]

Previous pooled data (2003) from phase I to III studies of omalizumab showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%).[10] These findings are reflected in both the European Union and US labels for omalizumab.[1,2] The biological plausibility of free IgE reduction or indeed allergic disease itself as a cause of malignancy has not been established[11-16]; nevertheless, because of labeled information, the possible association between omalizumab therapy and malignancy remains a concern for clinicians and patients.[17,18]

Two further strategies have been undertaken since 2003 to assess the possible association between omalizumab and malignancy risk. First, a US-based 5-year registry of more than 7000 omalizumab-treated and non–omalizumab-treated patients with moderate-to-severe persistent allergic asthma (the EXCELS study) was initiated to evaluate omalizumab's long-term safety and clinical effectiveness[19]; this registry is ongoing. Second, since the original analysis, the omalizumab clinical trial database has expanded considerably, and this has allowed for a more robust analysis to be performed. This article presents the results of the recent pooled analysis of 67 clinical trials of omalizumab conducted over 2 decades.

METHODS

Study designs and analysis populations

All clinical trials of omalizumab conducted by either sponsor company (Novartis or Genentech) with available data were considered eligible and included in this analysis. In total, data from 67 completed phase I to IV trials

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Abbreviations used
AE: Adverse event
NMSC: Nonmelanoma skin cancer
RDBPC: Randomized, double-blind, placebo-controlled

investigating the efficacy, tolerability, and safety of omalizumab were included in the pooled analysis (see Table E1 in this article's Online Repository at www.jacionline.org). Data collected in follow-up studies (eg, during extension periods) were captured as part of the original trial. Studies were included if patients received intravenous or subcutaneous omalizumab, regardless of the dose, formulation, (lyophilized or liquid), or dosing frequency (single-dose studies were included). Patients were either randomized within a controlled trial (with a placebo or active control arm) or received omalizumab in a single-arm study. Registry, postmarketing surveillance, or compassionate-use studies were excluded, but continuous-access extensions to controlled trials were included. In addition, each clinical trial had to be conducted by the sponsor companies, so that individual patient-level data were available. Patients with a prior history of malignancy were included in 11 clinical trials, which corresponded to those completed before registration; later studies excluded patients with a history of prior malignancy.

All analyses considered the number of patients with events and not the number of events. Assessments are presented for 3 study cohorts. The prespecified primary analysis group comprised patients from randomized, double-blind, placebo-controlled (RDBPC) trials (32/67 studies). RDBPC trials were considered least prone to bias because randomization ensures balance of baseline characteristics and adverse events (AEs) are reported in a blinded fashion. The "controlled clinical trials" group comprised patients from RDBPC trials and any other controlled trial whether blinded, unblinded, randomized, or allocated (40/67 studies). The "all clinical trials" group comprised patients from all 67 eligible studies. This final cohort also included all patients in the controlled clinical trials population and any uncontrolled trials, such as those with a single-omalizumab arm only or any study with more than 1 omalizumab-treated arm but without any non–omalizumab-treated control arm. Patients who received placebo in a controlled clinical trial and subsequently received omalizumab in an extension study were counted in each respective treatment group for the appropriate time period.

In addition to the clinical trials database, the ARGUS safety database, which is a global Novartis safety and pharmacovigilance database, was used to capture additional events that occurred in patients exposed to omalizumab during the clinical trials after study termination. Occasionally, entries can be made into the ARGUS database after study completion but before unblinding; this can generate information for patients who were in the placebo or control arms. Typically, only patients receiving active treatment (omalizumab) were captured in the ARGUS database. All data collection occurred between 1994 and 2010 in clinical trials that had completed by February 28, 2010.

Patients

Patients were included in the analysis if they received at least 1 dose of study medication and provided any posttreatment data on or after their first treatment date. Studies included patients with asthma (atopic and nonatopic), allergic rhinitis, atopic dermatitis, and urticaria, and patients undergoing immunotherapy.

Identification of malignant events

A comprehensive clinical and statistical analysis of malignancies observed across all clinical trials was undertaken. Any AE with a start date on or after the patient's date of first study medication in any clinical trial or phase was considered. No cutoff was applied, and thus all events on or after the first dose of medication were considered when reported (ie, patients entering a follow-up study or events that occurred in the transition between clinical trials were included). All AEs identified from the clinical trial database had been reported by an investigator through the sponsor's data collection systems as part of routine data collection in the clinical trial. In addition, a search of the ARGUS database was conducted to increase the capture of potential malignancies. The ARGUS search identified additional AEs in predominantly omalizumab-treated patients that occurred after the clinical trials had ended and includes events even if they occur substantively after the last exposure to treatment within a clinical trial, in which case the clinical trial database will have closed (there is no time limit for recording events within ARGUS). The combined search of the clinical trial database and the ARGUS database ensures the most complete case ascertainment.

AEs were categorized by using the Medical Dictionary for Regulatory Activities (version 13.0) either at the time the study was reported or coded during the data pooling work (see Fig E1 in this article's Online Repository at www.jacionline.org). Potential malignancies in the pooled dataset were identified by means of a Standardized Medical Dictionary for Regulatory Activities Query search for "malignancy" or by a System Organ Class search for "neoplasms benign, malignant and unspecified (including cysts and polyps)."

For all potential cases identified, blinded patient narratives were initially screened by a physician from each sponsor company to eliminate cases clearly not related to malignancy, such as benign nevi. Only cases in which both reviewers agreed that the event was clearly a benign condition were excluded from analysis. The remaining cases were reviewed by an external independent oncology panel ("adjudication panel"), also in a blinded fashion, to confirm the event as a primary malignancy. Both "definite" and "possible" cases of malignancy were included as events to ensure all potential events were captured in the analysis. Recurrent malignancies or metastasis of pre-existing malignancies were not included as events; a new-onset malignancy that presented with metastasis was included.

The first study-emergent primary malignancy occurring in a patient was recorded, which included the specific malignancy type. Events that were assessed as malignancies in the previous pooled analysis were recorded as malignancies in the present analysis; no further adjudication was carried out on these events (ie, the status of events considered malignant remained unchanged).

An additional analysis of primary malignancies was performed, which excluded nonmelanoma skin cancer (NMSC). Because NMSC is one of the most common forms of cancer worldwide, patients who attend frequent clinic visits within clinical trials might have a greater likelihood of reporting skin changes as part of a routine visit. Because NMSC has a specific set of known risk factors (eg, fair skin complexion, age >40 years, sun exposure, and sunburn), an analysis excluding this more common cancer was performed.

Statistical analysis

The primary analysis assessed the incidence of primary malignancy in the RDBPC trials, recorded as the number of patients with a malignancy and not the number of events and accounted for observation time. Observation time is the time from the date of first study drug administration to the latest date available for a patient, censored at the first malignancy event date if such an event is observed, and was not restricted to the time the patient was receiving study medication (this is the exposure to study medication). The overall incidence rate for malignancy events was calculated per 1000 patient-years from the number of patients with malignancies/observation time in patient-years, with exact 95% CIs. Exact 95% CIs for the rate ratio of the omalizumab versus placebo or control groups were also calculated, along with the 95% CIs for the rate difference. Kaplan-Meier curves for the time to first diagnosed malignancy are presented, and a log-rank test was used to compare the treatment groups. A Cox proportional hazards model was used to estimate the hazard ratio. The incidence of primary malignancies was also summarized by age at baseline (<18, 18-64, and ≥65 years), sex, and total IgE level at baseline for both treatment groups. After excluding patients in single-dose studies, duration of exposure to study medication for omalizumab-treated patients and categorical cumulative dose of omalizumab (900 to ≤1950, >1950 to ≤3900, and >3900 mg) was assessed; the categorical cumulative dose analysis used a cumulative dose of 900 mg or less of omalizumab as the reference category. Additional statistical methodology can be found in the Methods section in this article's Online Repository at www.jacionline.org.

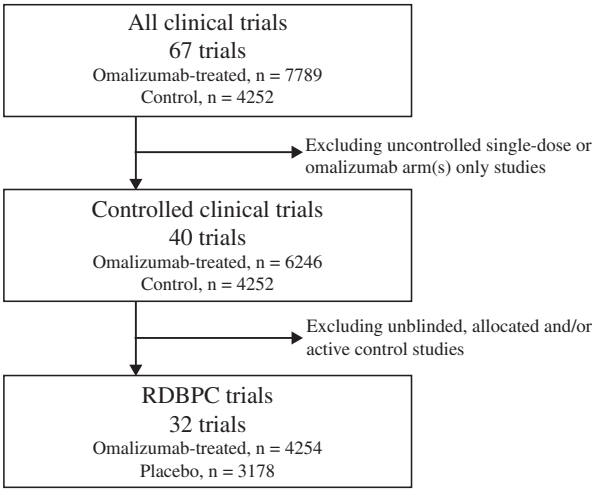

FIG 1. Number of patients included within each study cohort.

RESULTS

Patients

There were 11,459 unique patients in the entire clinical trials cohort (67 studies; 7,789 patients received omalizumab), 9,424 patients in controlled clinical trials (40 studies; 6,246 patients received omalizumab), and 7,432 patients in RDBPC trials (32 studies; 4,254 patients received omalizumab; Fig 1). The total duration of treatment exposure for omalizumab-treated and control/placebo-treated patients, respectively, were 5,800 and 2,168 patient-years in all clinical trials, 2,978 and 2,168 patient-years in controlled clinical trials, and 2,144 and 1,689 patient-years in RDBPC trials. The majority of clinical trials evaluated the efficacy and tolerability of omalizumab in patients aged 12 years or greater, and greater than 70% of patients across all studies had allergic asthma. Patients' demographics and baseline characteristics for all clinical trials and RDBPC trials are shown in Table I. Overall, treatment groups were well balanced.

TABLE I. Patients' demographics and baseline characteristics

	RDBPC trials*		All clinical trials	
Parameter	Omalizumab (n = 4254)	Placebo (n = 3178)	Omalizumab (n = 7789)	Control† (n = 4252)
Sex, no. (%)				
Male	2005 (47.1)	1369 (43.1)	3560 (45.7)	1842 (43.3)
Female	2249 (52.9)	1809 (56.9)	4229 (54.3)	2410 (56.7)
Race, no. (%)				
White	3324 (78.1)	2431 (76.5)	5918 (76.0)	3171 (74.6)
Black	359 (8.4)	246 (7.7)	678 (8.7)	336 (7.9)
Other	326 (7.7)§	252 (7.9)‖	523 (6.7)§	306 (7.2)‖
Age (y),‡ no. (%)				
<12	690 (16.2)	365 (11.5)	924 (11.9)	417 (9.8)
12-17	349 (8.2)	258 (8.1)	539 (6.9)	314 (7.4)
18-64	3078 (72.4)	2437 (76.7)	6012 (77.2)	3354 (78.9)
≥65	137 (3.2)	118 (3.7)	314 (4.0)	167 (3.9)
Mean (SD)	32.3 (16.7)	34.9 (16.8)	35.1 (16.8)	36.0 (16.6)
IgE (IU/mL)				
Mean (SD)	254 (261)	235 (231)	230 (231)	229 (231)
Smoking status, no. (%)				
Current smoker	82 (1.9)	68 (2.1)	151 (1.9)	72 (1.7)
Not current smoker¶	2584 (60.7)	2196 (69.1)	3419 (43.9)	2342 (55.1)
Status not recorded	1588 (37.3)	914 (28.8)	4219 (54.2)	1838 (43.2)

*Demographics/baseline characteristics in the controlled clinical trials were similar to those in the RDBPC trials.
†Placebo or standard therapy control.
‡Age at start of study.
§Data missing for 20 patients.
‖Data missing for 11 patients.
¶Total for "not current smoker" includes patients recorded as having never smoked, exsmokers, and not current smokers.

AEs and adjudication of malignancies

Across all of the 67 clinical trials, 63,011 AEs were reported. From these, Standardized Medical Dictionary for Regulatory Activities Query and System Organ Class searches from the clinical trial and ARGUS safety databases identified 177 patients with a total of 209 potential malignancies. After blinded internal screening, 47 events were judged to be nonmalignancies (excluded events are detailed in the Results section in this article's Online Repository at www.jacionline.org). Of the remaining 162 events, external adjudicators identified 56 patients (43 in the omalizumab-treated group and 13 in the control group) with a total of 62 malignancies; 12 of 56 patients were identified from the ARGUS database (11 in the omalizumab-treated group and 1 in the control group).

Analysis of malignant events

Including patients with events identified from the ARGUS database. The primary analysis identified primary malignancies in 25 patients in RDBPC trials: 14 in 4254 omalizumab-treated patients and 11 in 3178 placebo-treated patients. The incidence rates per 1000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 (95% CI, 2.26-6.94) and 4.45 (95% CI, 2.22-7.94), respectively, with a corresponding rate ratio of 0.93 (95% CI, 0.39-2.27; Table II). Primary malignancy incidence rates in all clinical trials, which included uncontrolled trials, and in controlled clinical trials were similar to those in RDBPC trials; corresponding rate ratios were numerically higher (see Table E2 in this article's Online Repository at www.jacionline.org).

The 2 most frequently reported primary malignancies in omalizumab-treated patients in RDBPC trials were NMSC (n = 5) and melanoma (n = 2), and in placebo-treated patients these were NMSC (n = 2) and testicular neoplasm (n = 2; Table III). The time to primary malignancy was similar in omalizumab-treated patients and placebo-treated patients (Fig 2). The hazard ratio from the adjusted Cox model was 1.00 (95% CI, 0.36-2.77), and the log-rank *P* value was .44.

There was no evidence that a greater duration of exposure to omalizumab was related to increased malignancy risk (odds ratio, 0.82 [95% CI, 0.68-0.98] per 30-day increment of exposure; Table IV). There was also no indication of a dose-response relationship between omalizumab and malignancy (categorical cumulative dose analysis, Table IV). There was a low incidence of primary malignancy within subgroups as assessed by sex, age, and IgE levels at baseline (data not shown).

NMSCs were identified in 7 patients (5 in the omalizumab-treated group and 2 in the placebo-treated group). Excluding these

TABLE II. Incidence of primary malignancy in RDBPC trials (primary analysis, including events identified from the ARGUS database)

	Omalizumab (n = 4254)	Placebo (n = 3178)	Omalizumab vs placebo	
			Difference in rates	Rate ratio
No. of patients with primary malignancy	14	11		
Observation time (y)	3382.40	2473.79		
Incidence rate*	4.14	4.45	−0.31	0.93
95% CI	2.26 to 6.94	2.22 to 7.94	−4.47 to 3.35	0.39 to 2.27

*Incidence rates presented are per 1000 patient-years of observation time (number of patients with malignancies/observation time in patient-years censored at the date of primary malignancy).

patients with NMSCs from the analysis, the incidence rates per 1000 patient-years of observation time were 2.66 (95% CI, 1.22-5.04) and 3.64 (95% CI, 1.66-6.89) for omalizumab-treated and placebo-treated patients, respectively, with a rate ratio of 0.73 (95% CI, 0.26-2.08).

Excluding patients with events identified from the ARGUS database. Incidence rates per 1000 patient-years of observation time for omalizumab- and placebo-treated patients in RBDPC trials, excluding ARGUS events, were 3.25 (95% CI, 1.62-5.81) and 4.45 (95% CI, 2.22-7.94), respectively, with a corresponding rate ratio of 0.73 (95% CI, 0.29-1.86; see Table E3 in this article's Online Repository at www.jacionline.org). The time to primary malignancy excluding ARGUS events was similar to that for the primary analysis population (data not shown).

DISCUSSION

The benefits of omalizumab for the treatment of severe persistent allergic asthma have been well established in clinical trials.[20-29] The potential risk of malignancy, however, has remained a concern for clinicians and patients. In this pooled analysis of 67 clinical trials, no association was observed between omalizumab treatment and the risk of malignancy in the primary analysis group (RDBPC trials), which included events captured in the ARGUS safety database (rate ratio below unity, 0.93). Inclusion of AEs from ARGUS, which captured events mostly from omalizumab recipients after the clinical trials had completed and without a time limit, provides a thorough and very conservative examination of malignancies in patients receiving the drug. Because ARGUS data added patient time only for patients who had malignancy events and captured omalizumab-treated patients nearly exclusively, this analysis inflates the risk ratio compared with the analysis without ARGUS and represents the most conservative estimate. Consequently, the analysis of primary malignancies in the RDBPC trials that excluded additional events identified from ARGUS resulted in a lower and possibly more accurate rate ratio of 0.73. In addition, the primary malignancies identified in patients enrolled in RDBPC trials were of varying histologic type and occurred in a number of different organ systems with no cluster of histologies. An additional assessment excluding NMSCs from the primary analysis also found no difference in the risk of malignancy in omalizumab-treated patients compared with control subjects, with the incidence rate higher in control

TABLE III. Summary of primary malignancy type (RDBPC trials,* including events identified from the ARGUS database)

Primary malignancy	Omalizumab (n = 4254)	Placebo (n = 3178)
Any event, no. (%)†	14 (0.33)	11 (0.35)
NMSC	5 (F30, F46, F66, F75, M74)	2 (F56, M66)
Breast	1‡ (F47)	—
Melanoma	2 (F39, F44)	—
Prostate	1 (M74)	—
Colon	—	1 (M57)
Salivary gland	1‡ (M44)	—
Neoplasm	1 (F38)	—
Pancreatic cancer	1 (M68)	—
Rectal cancer	1 (F44)	—
Brain neoplasm	—	1 (F27)
Gastric cancer	—	1 (M64)
Lung adenocarcinoma	—	1 (M36)
Esophageal carcinoma	—	1 (M56)
Renal neoplasm	—	1 (F6)
Medulloblastoma	—	1 (M7)
Bladder	1‡ (M47)	—
Testicular neoplasm	—	2 (M21, M34)

F, Female (followed by age in years); *M*, male (followed by age in years).
*Primary malignancy types in the all clinical trials cohort were consistent with those in RDBPC trials.
†Patients were counted only once for a given type of malignancy.
‡Malignancies reported to the ARGUS database.

subjects. It is not possible to draw any conclusions based on baseline characteristics of sex, age, and IgE levels at baseline because of a low incidence of primary malignancy within subgroups. In summary, these analyses do not support a relationship between omalizumab treatment and malignancy.

RDBPC trials are more robust and less prone to bias than other clinical trials because of the randomization procedure and the blinded reporting of AEs. Consequently, RDBPC trial estimates of risk are the most accurate. In this pooled analysis the malignancy rate ratio for omalizumab-treated patients versus control subjects was also calculated for the less robust groupings of all clinical trials, including uncontrolled studies (rate ratio, 1.35) and controlled clinical trials (rate ratio, 1.13); these malignancy rate ratios were numerically higher than in RDBPC trials. However, there are several contributing factors that can explain the higher risk ratio. Given the nature of clinical trials included in the all clinical trials group (eg, uncontrolled studies with an omalizumab arm only), patients taking omalizumab were followed up for much longer than control subjects (7222 vs 3010 patient-years). In addition, the all clinical trials group included a number of open-label studies, which might have introduced bias in the reporting of AEs. The evidence does not support a relationship between omalizumab and malignancy risk.

This pooled analysis included large numbers of patients followed for a long period of time and provides a more precise and robust estimate of a malignancy risk compared with the previous evaluation in 2003.[10] In the current analysis the rate ratio is lower compared with that in 2003, and the associated CIs are narrower (Fig 3). Furthermore, external adjudication of malignant events and the inclusion in the current analysis of both "definite" and "possible" events as malignant events allowed for a thorough and unbiased assessment of the incidence of malignancy in these patients.

On the basis of the current analysis, a causal effect of omalizumab on the incidence of malignancy is unlikely. The

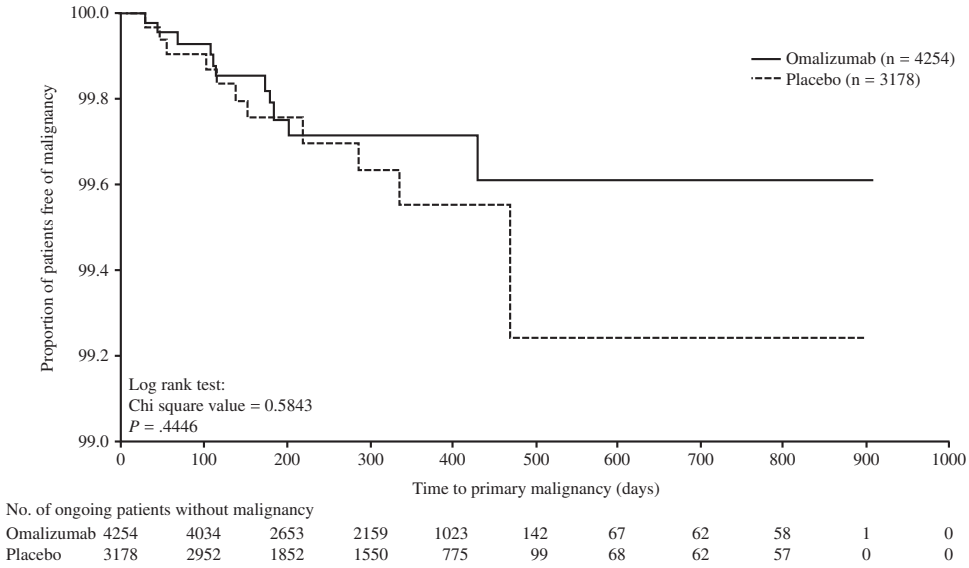

FIG 2. Time to primary malignancy in RDBPC trials (y-axis, >99.0%).

TABLE IV. Incidence of primary malignancy by duration of exposure to study medication and by categorical cumulative dose of omalizumab (RDBPC trials, including events identified from the ARGUS database, n = 4185)

	Omalizumab
Exposure to omalizumab (d)	
Mean (SD)	186.9 (112.00)
Mean (SD) censored at time of primary malignancy	186.7 (111.98)
OR* (95% CI)	0.99 (0.99-1.00)
Categorical cumulative dose of omalizumab† (mg)	
OR (95% CI)	
900 to ≤1950	1.25 (0.31-5.02)
>1950 to ≤3900	0.28 (0.03-2.54)
>3900	1.77 (0.48-6.63)

OR, Odds ratio.
*Odds ratio for having a primary malignancy for each extra day of exposure to omalizumab treatment. The odds ratio for each extra day of exposure was used to derive an odds ratio per 30 days of exposure to omalizumab treatment (odds ratio, 0.82; 95% CI, 0.68-0.98). Note: Cumulative treatment exposure duration (sum of all exposures for all patients in RDBPC trials) for omalizumab-treated patients (n = 4254) was 2143.9 patient-years, and that for placebo patients (n = 3178) was 1689.1 patient-years. Cumulative dose of omalizumab was not analyzed as a continuous variable because of lack of a linear relationship.
†A cumulative dose of 900 mg or less of omalizumab was used as the reference category.

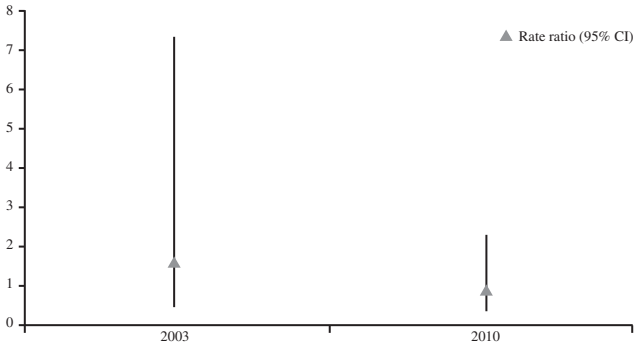

FIG 3. Primary malignancy rate ratio in the previous (year 2003) and current (year 2010) analysis (RDBPC trials).

primary analysis risk ratios were not increased, and these results were consistent with the analysis excluding NMSC. The biologic plausibility for IgE blockade and malignancy onset has not been established.[11-16] Furthermore, the lack of an exposure-response relationship also does not support a causal association between omalizumab treatment and malignancy.[30,31]

This pooled analysis has several limitations. Although the results of the primary analysis do not show an association between omalizumab therapy and malignancy (rate ratio, 0.93) and the associated CIs are narrower than in the 2003 analysis, they remain relatively wide (95% CI, 0.39-2.27), and a modest increase in the risk of malignancy cannot be completely ruled out with this sample size and observation time. Malignancy was a rare event overall, and it required analysis of global studies conducted over 2 decades to achieve this degree of precision. Furthermore, most of the studies included in this analysis had a short duration of follow-up, and the effect of longer-term omalizumab therapy cannot be fully assessed. Both open-label and uncontrolled clinical trials are subject to reporting bias (with increased reporting of AEs in omalizumab-treated patients); in addition, single-arm extensions provide a greater opportunity for AE reporting in omalizumab-treated patients. Malignancy was not a predefined AE of special interest, and in some cases suboptimal clinical information was available for adjudication. To address this limitation, conservative judgments were made to avoid misclassification; any case that was a possible malignancy was included as a true malignancy in the subsequent analyses. The majority of the 67 clinical trials (56 trials) excluded patients with a prior history of malignancy to prevent inclusion of patients who might have had an unreported active malignancy at baseline; there was a low incidence of primary malignancy within subgroups, as assessed in RDBPC trials that had or did not have exclusion criteria for patients with a pre-existing malignancy (data not shown); it was therefore not possible to draw any conclusions based on a prior history of malignancy. Specific conclusions were also not possible in

pediatric, elderly, or nonwhite patients because of the small size of these subgroups. Data about prior smoking history were also insufficient to analyze its effect on cancer risk.

In general, the incidence of cancer observed in our pooled analysis was similar to that observed for other populations. For example, the observed cancer incidence in the RDBPC trial group (4.14 and 4.45 per 1000 person-years for omalizumab and placebo groups, respectively) was in the range of the incidence reported from a population-based cohort study of asthmatic patients (5.9 per 1000 person-years) and nonasthmatic patients (4.1 per 1000 person-years).[32] This pooled analysis was also generally consistent with the overall cancer incidence from the US Surveillance Epidemiology and End Results registry (4.6 per 1000 person years).[33] However, these comparisons are methodologically limited because of differences in the age, sex, race, and geographic structure of these populations compared with our pooled analysis.

Additional omalizumab long-term safety data will come from the 5-year EXCELS study, which will specifically evaluate the incidence of all malignant tumors and other serious AEs reported from greater than 7000 patients with moderate-to-severe persistent allergic asthma in a real-world clinical practice setting.[19] Results from an interim analysis, comprising 18,860 patient-years in the omalizumab-treated group and 10,947 patient-years in the non–omalizumab-treated treated group, showed similar malignancy incidence rates in the omalizumab-treated (12.78; 95% CI, 11.22-14.50) and non–omalizumab-treated (14.48; 95% CI, 12.21-17.04) cohorts. The corresponding rate ratio was 0.88 (95% CI, 0.65-1.19).[34] Final results of the EXCELS study are expected in 2012.

In conclusion, the omalizumab clinical study program provides a large amount of data on the efficacy, tolerability, and safety of omalizumab therapy. The results of this current pooled analysis found no association between omalizumab treatment and the risk of malignancy in RDBPC trials and suggest that a causal relationship between omalizumab therapy and malignancy is unlikely. The current analysis adds to the increasing body of clinical evidence supporting the long-term safety of omalizumab therapy. This, combined with the established efficacy profile of omalizumab, continues to support a favorable risk/benefit profile of the drug.

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Clinical implications: In this pooled analysis no associations were observed between omalizumab treatment and malignancy risk in the primary analysis group (RDBPC trials), supporting the safety of omalizumab therapy.

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METHODS

Statistical analysis

Analysis of the occurrence of malignancy AEs accounted for the observation time of each patient. For a patient who experienced a malignancy AE, the observation time was curtailed at the date of the primary malignancy. Patients who did not report a primary malignancy were censored at the end of their observation time. The end of exposure to study medication was the last available study treatment date (for omalizumab-treated and placebo-treated patients) or the date of the last assessment visit in a non–follow-up study (for patients receiving nonplacebo control, for whom treatment dates were not recorded).

In addition to an unadjusted model with treatment as the only covariate, an adjusted model was fitted considering the baseline covariates of age, total IgE level at baseline (quartiles), and duration of exposure to study medication (curtailed at the time of primary malignancy).

The odds ratio within the omalizumab treatment group was calculated for both exposure to omalizumab and categorical cumulative dose of omalizumab.

RESULTS

AEs and adjudication of malignancies

Forty-seven events were judged as nonmalignancies: 21 (44.68%) were benign obstetric and gynecologic conditions (leiomyomas, uterine fibroids, increased size uterine fibroids, and elective tubectomy); 21 (44.68%) were benign dermatologic conditions (warts, skin papillomas, and melanocytic nevus); and 5 (10.64%) were in the "other" category (mycosis fungoides code that, after review, were determined to be a fungal infection, uvula polyp, and 3 lipomas).

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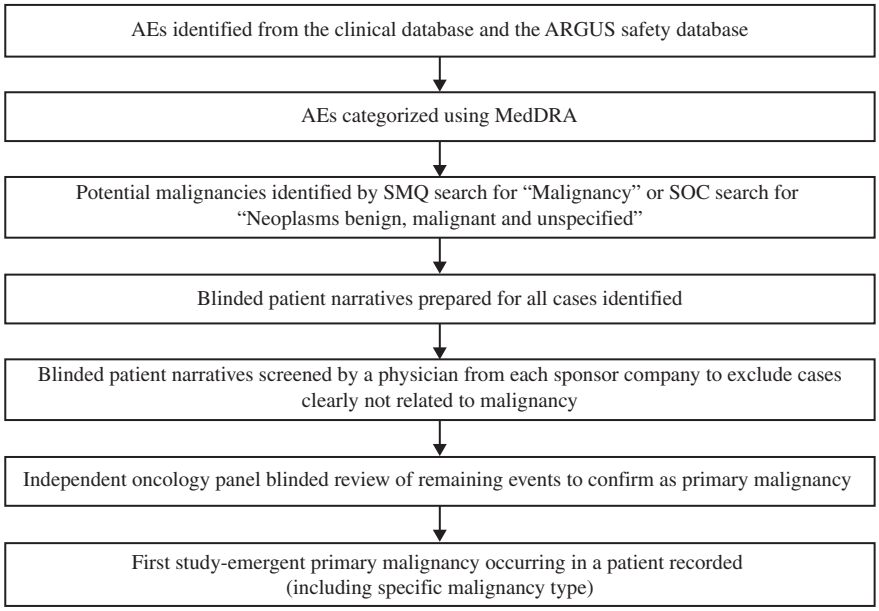

FIG E1. Identification of malignant events. *ARGUS*, Global pharmacovigilance database maintained by Novartis; *MedDRA*, Medical Dictionary for Regulatory Activities; *SMQ*, Standardized Medical Dictionary for Regulatory Activities Query; *SOC*, System Organ Class.

TABLE E1. Studies included in the pooled dataset

Study no.	FPFV	Sponsor	Design
006[E1]	1997	Novartis	RDBPC
006 E[E2]	1998	Novartis	Open-label, omalizumab only
007[E3]	1998	Novartis	RDBPC
008[E4]	1998	Novartis	RDBPC
009[E5]	1998	Novartis	RDBPC
010[E6]	1998	Novartis	RDBPC
010 E[E7]	1998	Novartis	Open-label, omalizumab only
010 E1[E8]	1999	Novartis	Open-label, omalizumab only
011[E9]	1998	Novartis	RDBPC
011 E1[E10]	2000	Novartis	Open-label, omalizumab only
011 E2[E11]	2002	Novartis	Open-label, omalizumab only
011 E3[E12]	2003	Novartis	Open-label, omalizumab only
0112[E13]	1999	Novartis	RDBPC
0113*	2001	Novartis	Randomized, investigator-blind, placebo-controlled†
0114[E14]	1999	Novartis	RDBPC
IA04[E15]	2000	Novartis	Randomized open-label omalizumab vs current asthma treatment
IA04 E1*	2002	Novartis	Open-label, omalizumab only
IA04 E2*	2003	Novartis	Open-label, omalizumab only
A2303[E16]	2001	Novartis	RDBPC
2304[E17]	2001	Novartis	RDBPC
2306[E18]	2001	Novartis	RDBPC
IA05[E19]	2004	Novartis	RDBPC
2425[E20]	2005	Novartis	Randomized open-label omalizumab vs optimized asthma therapy
2203*	2001	Novartis	Randomized, open-label comparing 2 forms of omalizumab, single-dose
2204[E21]	2003	Novartis	Randomized, open-label comparing 2 forms of omalizumab, single-dose
2204[E1]*	2005	Novartis	Randomized, open-label comparing 2 forms of omalizumab, single-dose
2206*	2005	Novartis	Nonrandomized, open-label comparison of 2 populations both receiving the same omalizumab regimen, single-dose
2208[E22]	2007	Novartis	Nonrandomized, open-label PK study in omalizumab
2210[E23]	2008	Novartis	RDBPC
C2101[E24]	2007	Novartis	Randomized, open-label PK comparison of 3 omalizumab forms, single-dose
C2303[E25]	2007	Novartis	Single-arm, open-label
1101*	1999	Novartis Japan	Randomized single-blind, placebo-controlled PK, single-dose
1301*	2001	Novartis Japan	RDBPC
1303[E26]	2001	Novartis Japan	RDBPC
1304[E27]	2003	Novartis Japan	RDBPC
1305[E28]	2002	Novartis Japan	Randomized, double-blind, double-dummy comparison of omalizumab with suplatast tosilate
1306*	2002	Novartis Japan	Single-arm, open-label
1307[E29]	2003	Novartis Japan	Single-arm, open-label
D01[E30]	1999	Novartis Germany	RDBPC
DE03[E31]	2006	Novartis Germany	RDBPC
DE03 E7	2007	Novartis Germany	Open-label, rush immunotherapy treatment only (no placebo or omalizumab)
DE03 E8	2008	Novartis Germany	Open-label, rush immunotherapy treatment only (no placebo or omalizumab)
DE05[E32]	2007	Novartis Germany	RDBPC
FR01[E33]	2001	Novartis France	RDBPC
FR01 E[E33]	2001	Novartis France	Open-label, omalizumab only
FR02[E34]	2007	Novartis France	RDBPC
US23[E35]	2005	Novartis USA	RDBPC
Q0572g‡	1994	Genentech	Nonrandomized, open-label, controlled, PK, single-dose
Q0619g‡	1994	Genentech	Nonrandomized, open-label PK study in omalizumab
Q0624g[E36]	1994	Genentech	RDBPC
Q0626g‡	1994	Genentech	Randomized single-blind, placebo-controlled PK.
Q0630g[E37]	1994	Genentech	RDBPC
Q0634g[E38]	1994	Genentech	RDBPC
Q0637g[E39]	1994	Genentech	Randomized single-blind, placebo-controlled PK
Q0673g[E40]	1995	Genentech	Randomized, open-label, comparing doses of omalizumab
Q0694g[E41]	1996	Genentech	RDBPC
Q0723g‡	1996	Genentech	Randomized, open-label PK, comparing routes of omalizumab administration
Q2143g‡	2000	Genentech	CAT controlled, open-label
Q2195g‡	2001	Genentech	Single-arm, open-label
Q2461g‡	2002	Genentech	Single-arm, open-label
Q2736g‡	2003	Genentech	Single-arm, open-label
Q2788g[E42]	2004	Genentech	RDBPC
Q3623g‡	–	Genentech	Single-arm, open-label
Q3662g[E43]	2006	Genentech	RDBPC
Q4160g‡	2008	Genentech	RDBPC
Q4229n[E44]	2007	Genentech	RDBPC
Q4577g[E45]	2009	Genentech	RDBPC, single-dose

The Suffix "E" refers to an extension study.
CAT, Current asthma treatment; *FPFV*, First patient first visit; *PK*, pharmacokinetic.
*Novartis, data on file.
†Study 0113 is described as investigator blind, but the study methodology looks like any RDBPC in the program.
‡Genentech, data on file.

TABLE E2. Incidence of primary malignancy in all clinical trials (including uncontrolled studies) and controlled clinical trials (including events identified from the ARGUS database)

	Omalizumab	Placebo	Difference in rates	Rate ratio
All clinical trials	n = 7789	n = 4252		
No. of patients with primary malignancy	39	12		
Observation time (y)	7222.02	3010.05		
Incidence rate*	5.40	3.99	1.41	1.35
95% CI	3.84 to 7.37	2.06 to 6.95	−2.11 to 4.16	0.69 to 2.85
Controlled clinical trials	n = 6246	n = 4252		
No. of patients with primary malignancy	20	12		
Observation time (y)	4447.92	3010.05		
Incidence rate*	4.50	3.99	0.51	1.13
95% CI	2.75 to 6.94	2.06 to 6.95	−3.09 to 3.67	0.52 to 2.54

*Incidence rates presented are per 1000 patient-years of observation time (number of patients with malignancies/observation time in patient-years censored at the date of primary malignancy).

TABLE E3. Incidence of primary malignancy in RDBPC trials (not including events identified from the ARGUS database)

	Omalizumab	Placebo	Difference in rates	Rate ratio
RDBPC trials	n = 4254	n = 3178		
No. of patients with primary malignancy	11	11		
Observation time (y)	3383.72	2472.51		
Incidence rate*	3.25	4.45	−1.20	0.73
95% CI	1.62 to 5.81	2.22 to 7.94	−5.26 to 2.27	0.29 to 1.86

*Incidence rates presented are per 1000 patient-years of observation time (number of patients with malignancies/observation time in patient-years censored at the date of primary malignancy).